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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,539	10/22/1999	NICHOLAS M. DEAN	ISIS-3013	7420

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EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/22/2002 23

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/403,539	Dean et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 8, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *27-29 and 34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *27-29 and 34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communications filed August 8, 2002 and September 17, 2002, Paper Nos. 19, 20 and 22.

Claims 27-29, 34 are pending in the instant application.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 8, 2002 has been entered.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The claimed priority for claims 27-29, 34 to Application 08/244,993 is denied because there was no disclosure or teaching of alimentary canal administration of antisense oligonucleotides comprising 2'-alkoxyalkoxy modifications in the claimed parent application 08/244,993.

Response to Arguments and Amendments

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections

Claims 27-28, 33, 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simon et al, Arnold, Jr. et al or Agrawal et al in view of Hanecak et al Vlassov et al and Milligan et al is hereby withdrawn in light of Applicants' arguments filed August 8, 2002, Paper No. 20.

Maintained Rejections

Claims 27-28, 33, 34 are provisionally rejected under the judicially created doctrine of double patenting for the reasons of record set forth in the Office action mailed August 8, 2001, Paper No. 15.

No arguments have been presented addressing this rejection.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-29, 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enhanced bioavailability of antisense oligonucleotides

comprising 2'-O-(2-methoxyethoxy) modifications (2'MOE) following alimentary administration, does not reasonably provide enablement for a method of modulating the expression of any and/or all target genes comprising the alimentary administration of anitsense oligonucleotides comprising 2'MOE modifications. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of modulating expression of any and/or all target genes in an organism comprising the alimentary administration of antisense oligonucleotides comprising 2'-$(O\text{-}CH_2\text{-}CH_2)_n$-O-alkyl modifications.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo

treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of modulating the expression of any and/or all target genes in an organism comprising the alimentary administration of antisense oligonucleotides comprising 2'-$(O\text{-}CH_2\text{-}CH_2)_n$-O-alkyl modifications. The specification teaches the enhanced bioavailability following alimentary administration of 2'-MOE gapped oligonucleotides compared to phosphorothioate containing, but non-2-MOE-containing oligonucleotides. The specification fails to teach the modulation in expression of any and/or all target genes in an organism comprising the administration of antisense oligonucleotides comprising 2'-$(O\text{-}CH_2\text{-}CH_2)_n$-O-alkyl modifications. One skilled in the art would not accept on its face the examples given in the specification of the enhanced bioavailability of antisense oligonucleotides comprising 2'-$(O\text{-}CH_2\text{-}CH_2)_n$-O-alkyl modifications following alimentary administration as being correlative or representative of the successful modulation in expression of any and/or all target genes in vivo comprising the alimentary administration of antisense oligonucleotides comprising 2'-$(O\text{-}CH_2\text{-}CH_2)_n$-O-alkyl modifications in view of the lack of guidance in the specification and known

unpredictability associated with the ability to predict the efficacy of antisense in modulating any and/or all target genes in an organism, whether those antisense oligonucleotides comprise stabilizing modifications or not. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with *in vivo* delivery and target gene modulation provided by antisense administered, and specifically regarding the instant compositions comprising antisense oligonucleotides comprising 2'-$(O\text{-}CH_2\text{-}CH_2)_n$-O-alkyl modifications.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods of modulating expression of any and/or all target genes in an organism comprising the alimentary administration of antisense oligonucleotides comprising 2'-$(O\text{-}CH_2\text{-}CH_2)_n$-O-alkyl modifications. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring any and/or all target genes in an organism comprising the alimentary administration of antisense oligonucleotides comprising 2'-$(O\text{-}CH_2\text{-}CH_2)_n$-O-alkyl modifications. Since the specification fails to provide any particular guidance for the successful modulation of any and/or all target genes in an organism comprising the alimentary administration of antisense oligonucleotides comprising 2'-$(O\text{-}CH_2\text{-}CH_2)_n$-O-alkyl modifications, and since determination of these factors for an antisense, with or without 2'-O-modifications, to

target and modulate the expression of a specific gene is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

October 15, 2002

KAREN LACOURCIERE
PATENT EXAMINER